MELANOMA

Digging around moles

Melanocytes are the cell of origin for benign melanocytic naevi (moles) and melanomas, collectively known as melanocytic neoplasms. Previous investigations have shown that oncogenic mutations in *BRAF* and *NRAS* — and also other members of the MAPK signalling pathway — are common. However, a subset of melanocytic neoplasms is not associated with mutations in these genes and Boris Bastian and colleagues have identified another oncogene that can lead to deregulated MAPK signalling in melanoctyes.

Previously, hypermorphic mutations of *Gnaq* and *Gna11*, which encode q class G protein α subunits that mediate G-protein-coupled receptor signalling, were separately shown to cause hyperpigmentation in mice. Van Raamsdonk and colleagues sequenced the coding region of *GNAQ* and *GNA11* in samples from benign and malignant melanocytic neoplasms and they found somatic mutations in *GNAQ* — but not *GNA11* — in blue naevi (bluish moles, 83%), malignant blue naevi (50%) and uveal melanomas (46%). The oncogenic mutations in these types of melanocytic neoplasms were hitherto unknown because they do not harbour mutations in *BRAF* or *NRAS*. In contrast to the mouse hypermorphic variants, the *GNAQ* mutations in human tumours all occurred in codon 209 (Q209L), which is the equivalent of Ras-Q61 (one of the three common sites of oncogenic mutation of Ras), and also resulted in constitutive activation.

Next, the authors showed that exogenous expression of GNAQ-Q209L in transformed (*hTERT*;*CDK4*^{R24C};*TP53*$^{D/D}$) melanocytes resulted in anchorage-independent growth, at efficiencies comparable to transfection of NRAS-Q61R. Moreover, they injected GNAQ-Q209L-expressing *hTERT*;*CDK4*^{R24C};*TP53*$^{D/D}$ melanocytes into nude mice and the tumours that developed morphologically resembled those of blue naevi. Owing to the consistent deregulation of MAPK signalling in melanocyte neoplasms, the authors investigated whether this pathway was also affected by GNAQ-Q209L. In *hTERT*;*CDK4*^{R24C};*TP53*$^{D/D}$ and primary melanocytes transfected with GNAQ-Q209L they showed that Erk phosphorylation was increased, which is consistent with MAPK pathway activation, probably owing to the activation of protein kinase C by GNAQ.

Therefore, *GNAQ* is an oncogene in melanocytes that behaves similarly to *NRAS* and *BRAF* oncogenic mutants and functions downstream of G-protein-coupled receptors to activate MAPK signalling. Uveal melanoma is an aggressive cancer with a 10 year survival rate of 50% and currently no effective treatment. The finding offers an opportunity for developing therapies targeting GNAQ or its downstream signalling pathways.

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